Exhibit B

Phase II Trial of OGX-011 in Combination with Docetaxel in Metastatic Breast Cancer

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Abstract

Purpose: Clusterin is an antiapoptotic protein activated in response to cellular stress. OGX-011 is a second-generation antisense oligonucleotide that inhibits clusterin expression. The primary objective of this phase II trial was to assess the safety and efficacy of the combination of OGX-011 and docetaxel for metastatic breast cancer.

Experimental Design: Women with measurable metastatic breast cancer and ≤1 chemotherapy regimen were eligible. Three loading doses of OGX-011 640 mg i.v. followed by weekly OGX-011 and docetaxel 75 mg/m^2 (every 3 weeks) were given. A two-stage design was used with a hypothesis of H_0 ≤35% and H_a ≥55%. Objective response in ≥6 of the first 14 patients was required for the trial to continue to the second stage.

Results: Fifteen patients were enrolled. A median of six cycles were delivered (range, 2-10). Five partial responses were confirmed for a 33% response rate (95% confidence interval, 11.8-61.6%) with a further 9 (60%) patients showing stable disease. The median duration of stable disease was 9.3 months. The median time to progression was 8 months (95% confidence interval, 5.62-9.43 months). Toxic effects were similar to those with single agent docetaxel. Although serum clusterin decreased on treatment, there was no relationship observed between the magnitude of decrease and response.

Conclusion: The combination of OGX-011 and docetaxel at 75 mg/m^2 is well tolerated and clinical activity was seen in these patients with metastatic breast cancer, but there was an insufficient number of responses to meet the criteria for proceeding to the second stage of accrual.

Metastatic breast cancer is a prevalent and, unfortunately, incurable disease with a median survival of ~18 to 24 months. It represents a significant health burden with an estimated 40,000 women worldwide dying annually from metastatic breast cancer (1). Although recent studies have shown improved survival of women presenting today with metastatic breast cancer, virtually all will eventually die from their disease (2-4). This improvement in survival of metastatic breast cancer is likely the result of the utilization of newer therapeutic agents in the treatment of metastatic breast cancer (4). However, there is still a strong need for therapeutic advances for this group of patients.

One class of chemotherapeutic agents with significant activity in the treatment of breast cancer is the taxanes. The mechanism of action of taxanes is through stabilization of microtubules thereby arresting cell growth at the G_2-M phase (5). Of the two current taxanes in clinical use, docetaxel (every 3 weeks) has been shown to be superior to paclitaxel (every 3 weeks) in a large phase III trial in metastatic breast cancer, with a documented response rate of 32% and a median time to progression of 5.7 months (6). Although clearly active, there remain a significant proportion of patients who do not benefit from taxane therapy.

Clusterin is an antiapoptotic protein expressed in a variety of human solid malignancies including breast cancer (7). A number of studies have shown clusterin to be associated with a poorer outcome in breast cancer (8, 9). More importantly, clusterin is up-regulated after therapeutic stress, including following chemotherapy, trastuzumab therapy, and hormonal therapy in preclinical breast cancer models (10-12). Taken together, clusterin would seem to be a rational therapeutic target to down-regulate as part of the therapy for breast cancer. OGX-011 (OncoGenex Technologies, Inc.) is a second-generation phosphorothioate antisense oligonucleotide that is complementary to the clusterin mRNA translation initiation

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Translational Relevance

This article will be of significant interest to both clinicians and researchers because it is one of the first such published clinical trials of a targeted agent to an antiapoptotic protein (clusterin) in combination with chemotherapy in breast cancer. Evading cell death (antiapoptosis) is one of the hallmarks of cancer. Drug development has and will continue to attempt to exploit this process inherent in cancer cells. Valuable lessons may be learned from this trial, in particular, the topic of end points relevant in such targeted trials and the strategy and decisions to proceed to expanding the study cohort and development of future trials. Furthermore, there was a correlative science component to the study assessing for changes in target, the apoptotic protein (clusterin), in the serum in relation to radiologic responses defined by the Response Evaluation Criteria in Solid Tumors.

site and strongly inhibits clusterin expression *in vitro* and *in vivo* (13). A phase I study in prostate cancer showed suppression of clusterin mRNA and protein as well as a dose-related decrement in clusterin serum levels. In a combination phase I trial, full doses of OGX-011 could be safely combined with docetaxel (14, 15). These observations led to the phase II study of OGX-011 in combination with docetaxel in the treatment of metastatic breast cancer, which we report here.

Materials and Methods

Study design. The National Cancer Institute of Canada Clinical Trials Group IND 164 trial was a multicenter phase II trial of OGX-011 in combination with docetaxel as first- or second-line chemotherapy for the treatment of advanced stage breast cancer. The primary objectives were to assess the clinical activity, as defined by the objective response rate, as well as the safety of this combination. Secondary objectives included multiple other end points of clinical activity (duration of response, time to disease progression, and overall survival) and the association of changes in serum clusterin levels during treatment with clinical response.

Patient population. All patients had documented evidence of metastatic or locally advanced breast cancer not curable by surgery, radiotherapy, or standard systemic therapies. There was no limit on the number of prior hormonal therapies but there was a limit of one prior chemotherapeutic regimen delivered for advanced breast cancer.

Inclusion criteria for study entry were age ≥18 y old; Eastern Cooperative Oncology Group performance status of 0 to 2; no prior taxanes for advanced disease (prior taxanes delivered for stage I-III breast cancer were allowed if ≥6 mo from last dose of adjuvant/neoadjuvant taxane); measurable disease as defined by the Response Evaluation Criteria in Solid Tumors; life expectancy ≥3 mo; adequate hematologic, hepatic, and renal functions (absolute granulocyte count >1.5 × 10^9/L, platelets >100 × 10^9/L, a normal bilirubin, serum creatinine <1.5× upper limit of normal, aspartate aminotransferase/alanine aminotransferase <1.5× upper limit of normal, and normal partial thromboplastin time and international normalized ratio); adequate approved means of birth control for women of childbearing age; and patients being accessible for treatment and follow-up.

Exclusion criteria included any of the following: pregnant or lactating women; symptomatic central nervous system metastases; systemic infection requiring parenteral antibiotics; chemotherapy or radiation within 4 wk of enrollment; concurrent treatment with other experimental/investigational drugs or anticancer therapy; preexisting peripheral neuropathy >grade 2; or treatment on therapeutic dose of anticoagulant therapy.

All women provided written informed consent before registration on trial. The study was conducted in accordance with the ethical principles that originated in the Declaration of Helsinki and with Research Ethics Board approval at each participating center. The trial was coordinated by the National Cancer Institute of Canada Clinical Trials Group central office (Kingston, Ontario, Canada).

Trial treatment. A loading dose of OGX-011 alone was given at a dose of 640 mg i.v. over 2 h on days -7, -5, and -3 of cycle 1. Following this loading dose schedule, OGX-011 was then given once weekly at 640 mg for all subsequent weeks. Docetaxel was delivered at a dose of 75 mg/m^2 i.v. once every 3 wk (Fig. 1). Each 3-wk period (except cycle 1, which was 4 wk in length) was defined as one cycle. OGX-011 was provided by OncoGenex Technologies for the purposes of this study.

Patients continued treatment for a maximum of 10 cycles of therapy or until objective disease progression (if occurring before cycle 10) or other events that necessitated withdrawal. Thereafter, patients were followed up until death. Patients who discontinued treatment before disease progression were followed until progression and/or death.

All patients were to be assessed clinically for toxicity weekly during the first cycle and then once every 3 wk thereafter while on therapy. Hematology and biochemistry panels were drawn weekly during the first cycle and then on day 1 of each subsequent cycle. Radiologic assessment of tumor response was done following every second cycle (every 6 wk). Confirmation of objective responses (partial or complete whichever occurred first) was required within 6 wk.

Serum clusterin analysis. Serum clusterin levels were measured at baseline; days 1, 8, 15, and 22; day off treatment (primary progressors only); and 4 wk after study treatment (entire cohort; both primary progressors and those stopping study treatment due to reaching maximal allowable cycles of therapy). For the baseline measurement, two samples were drawn (screening and day -7) and the mean of these two measurements was taken as the baseline value. The rationale for measurements on the day off treatment and 4 wk posttreatment was to assess clusterin levels in the presence and absence of the antisense oligonucleotide at progression and off therapy (regardless of reason), respectively.

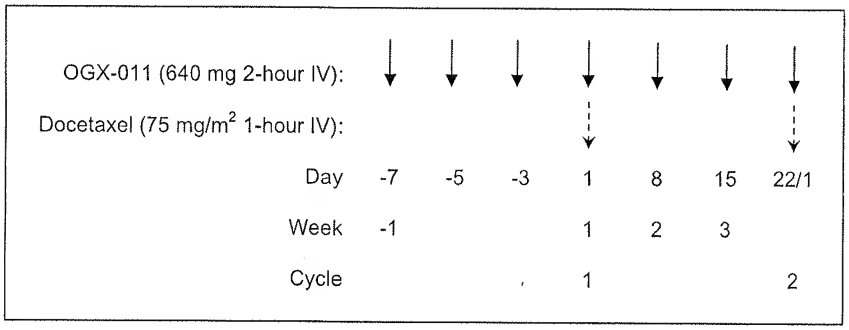

Fig. 1. Drug administration schedule.

Quantitative serum clusterin analysis was done with a solid-phase enzyme immunometric assay (ELISA) in microplate format with the BioVendor (2006) test kit. This ELISA uses two antihuman clusterin mouse monoclonal antibodies and a human serum–based calibrator. Calibrators, quality controls, and diluted samples were incubated in microtitration wells coated with the first antihuman clusterin monoclonal antibody. After a thorough wash, a biotin-labeled second antihuman clusterin monoclonal antibody was added to the wells and incubated with the immobilized antibody-clusterin complex. After a 1-h incubation and the subsequent washing step, streptavidin-horseradish peroxidase conjugate was added and incubated for 30 min. After the last washing step, the conjugate bound was allowed to react with the substrate (H_2O_2-tetramethylbenzidine). The reaction was then stopped by addition of an acid, and the absorbance of the resulting yellow product was measured spectrophotometrically at 450 nm. The absorbance is proportional to the concentration of clusterin.

The percent change from baseline (defined above) was calculated for each patient at each time point. The relationship between the decrease in clusterin at day 22 and objective response was assessed by logistic regression of percentage change in clusterin with response (*Y* versus *N*) as a dependent variable.

Statistical analysis. The primary end point of the study was the objective response rate. An objective response was defined as a patient having a best overall response of either complete response or partial response with confirmation criteria as per Response Evaluation Criteria in Solid Tumors (16). Stable disease in this study was defined as not achieving an objective response or not meeting the Response Evaluation Criteria in Solid Tumors definition for progressive disease, following two cycles of therapy. Time to progression and overall survival were defined as the time from registration to documented objective disease progression and death, respectively.

A two-stage design was used to evaluate the null hypothesis (H_0) that the true response rate is 35% versus the alternate hypotheses (H_a) that the true response rate was 55% (17). This was based on the assumption that the response rate in this population of patients (0-1 prior chemotherapy regimens for metastatic breast cancer) was likely to be ~35% with single agent docetaxel therapy, and we would not be interested in the combination of OGX-011 plus docetaxel if its true response rate was at this level or lower. Fourteen response evaluable patients would be entered in the first stage. If at the end of the first stage of accrual five or fewer responses were seen, the study would not proceed to the second stage. Otherwise, an additional 28 patients would be accrued to the study. The significance level (i.e., the probability of rejecting H_0 when it is true) was $\alpha = 0.05$ and the power (i.e., the probability of deciding the regimen is active) was 0.8 when the true response rate was 55%. The expected sample size with this design was 24 when the null hypothesis was true and 39 when the alternative hypothesis was true.

Results

Patients

A total of 15 patients from five Canadian centers were accrued to the first stage of the trial from October 2005 to April 2006, all of whom were evaluable for safety and response. Table 1 outlines the baseline characteristics of this patient population. The majority of the patients (87%) had a baseline performance status of 0 to 1. Eleven of the patients (73%) had estrogen receptor–positive disease. Ten patients had received prior chemotherapy, of which seven had received chemotherapy in the metastatic setting. Five patients had no prior chemotherapy as either adjuvant or metastatic therapy. Only one patient had received prior adjuvant taxane therapy. At the time of final data analysis, all 15 patients were off study treatment and the median follow-up was 18.2 months (range, 14.8-20.9).

Table 1. Patient characteristics

Patient characteristics (*N* = 15 patients)	No. of patients
Median age (range), y	51 (36-81)
Performance status (ECOG)	
0	7
1	6
2	2
Prior therapy	
None	5
Adjuvant chemotherapy	6
Chemotherapy for advanced/recurrent disease	7
Hormone therapy	12
Radiotherapy	14
Other therapy	3
Prior taxane	
No	14
Yes	1
No. of prior chemotherapy regimens	
0	5
1	7
2*	3
Sites of disease	
Abdomen	2
Adrenal	1
Bone	12
Breast	5
Chest wall	1
Kidney	1
Liver	9
Lung	6
Lymphangitic	1
Nodes	12
Pelvis	2
Pleural effusion	2
Skin	3
Spleen	1
Soft tissue	6
No. of sites of disease	
1	1
2	2
3	2
4 or more	10
Histology	
Infiltrating ductal	10
Mixed	3
Mucinous	1
Other	1
Hormone receptor status	
ER positive	11
PR positive	5
Both positive	5
Not done	1

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.
*Includes both adjuvant and metastatic chemotherapy regimens.

Treatment delivery and efficacy

A total of 86 cycles of docetaxel were delivered for all 15 patients, with a median of 6 cycles (range, 2-10). A total of 289 doses of OGX-011 were given, with a median of 20 doses per patient (range, 9-29). There were no complete responses in the 15 patients, but there were 5 confirmed partial responses for an overall response rate of 33% (95% confidence interval, 11.8-61.6%). The duration of response ranged from 2.7 to 7.3 months with a median of 4.9 months. An additional 9 (60%) patients showed stable disease with a median duration of stable disease of 9.3 months (range, 1.6-9.3 months). Only

one patient showed progressive disease following two cycles of study treatment. The degree of tumor shrinkage per individual patient over time for the 14 patients with a response or stable disease is illustrated in Fig. 2.

The median time to progression for the entire study cohort was 8 months (95% confidence interval, 5.62-9.43 months; Fig. 3). The median overall survival was not reached at the time of data analysis; however, the 75 percentile for overall survival was 11.1 months.

Tolerability. In general, the toxicity profile for the combination of OGX-011 and docetaxel was similar to that expected with single agent docetaxel (Table 2). The most common grade 3 or 4 toxicities were hematologic. All patients experienced either grade 3 (27%) or grade 4 (73%) neutropenia. Two patients experienced grade 3 anemia, whereas no patients had either grade 3 or 4 thrombocytopenia. Febrile neutropenia was documented in five patients.

The most common adverse effect related to the OGX-011 was rigors and chills (n = 12), which occurred primarily with administration of the initial few doses. Two patients had grade 2 and only one patient had grade 3 rigors/chills. Otherwise the most frequent grade 3 nonhematologic toxicities (likely related to the docetaxel) were fatigue (5 patients), peripheral edema (2 patients), arthralgias (2 patients), and dyspnea (2 patients). There were no grade 4 nonhematologic toxicities or treatment-related deaths.

Serum clusterin levels. All but one patient were evaluable for serum clusterin levels on days 8, 15, and 22. In general, serum clusterin levels decreased during OGX-011 therapy. The mean percent changes (relative to baseline) on days 8, 15, and 22 were -23.3%, -25.9%, and -32.1%, respectively; however, as shown in Fig. 4, there was considerable interpatient variability in the percent decrease. In the seven patients in whom off study values were available, the mean percent change from baseline clusterin was only -3.2%. By 4 weeks off study, clusterin levels were close to baseline (mean percent change, -3%) in the 10 patients in whom this measure was obtained. The magnitude of change from baseline in serum clusterin level at day 22 was not significantly related to objective response (odds ratio, 1.00; 95% confidence interval, 0.96-1.06).

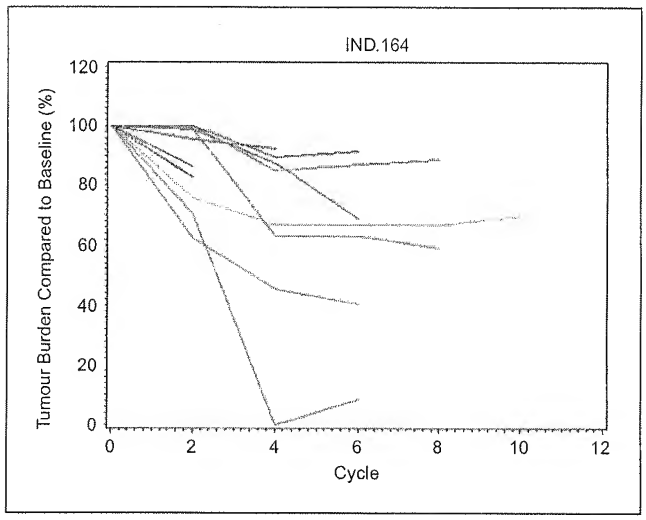

Fig. 2. Tumor shrinkage by individual patients.

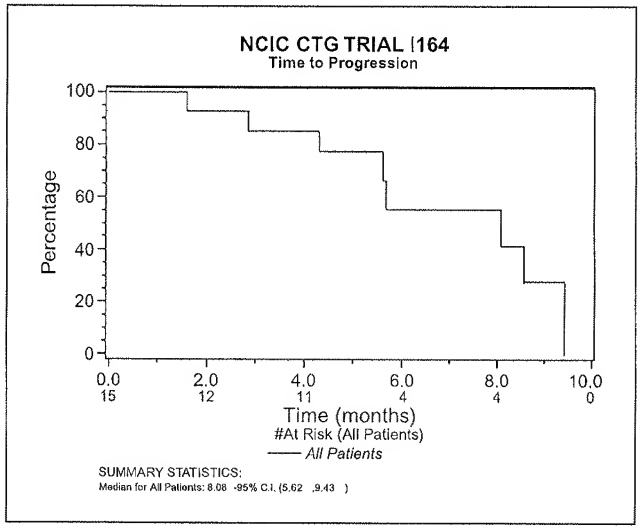

Fig. 3. Progression-free survival curve.

Discussion

One of the essential hallmarks of cancer is the ability to evade cell death (apoptosis; ref. 18). Although multiple targets and apoptotic pathways exist as therapeutic strategies, few have shown clinical success thus far. The first-in-man trial of OGX-011 delivered this antisense oligonucleotide to clusterin

Table 2. Grade 3 and 4 adverse events (all reported)

Adverse event	Grade	
	3	4
Fatigue	5	
Rigors/chills	1	
Anorexia	1	
Diarrhea	1	
Ileus	1	
Nausea	1	
Obstruction, ileum	1	
Vomiting	2	
Febrile neutropenia	5	
Infection (clinically documented), lung	1	
Infection with normal ANC, bladder	1	
Edema, limb	2	
Fracture	1	
Syncope	1	
Pain extremity, limb	1	
Pain head/headache	1	
Pain joint	2	
Pain neck	1	
Pain, other	1	
Dyspnea	2	
Irregular menses	2	
Thrombosis/thrombus/embolism	1	
Granulocytopenia	4	11
Hemoglobin	2	
Lymphopenia	7	1
Leukopenia	5	7

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

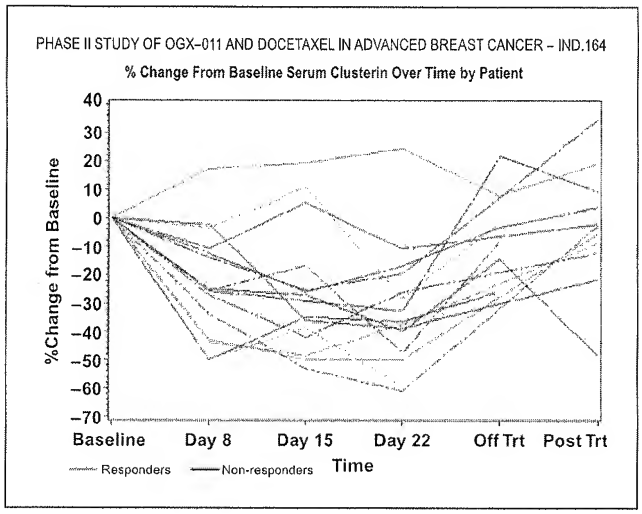

Fig. 4. Changes in serum clusterin level by individual patients.

preoperatively in 25 men with high-risk localized prostate cancer (14). This study showed that OGX-011 could be detected in prostate cancer tissue and led to dose-dependent decreases in clusterin expression and associated increases in the apoptotic index. In our study, we used a quantitative serum clusterin assay as a pharmacodynamic surrogate for target activity of OGX-011. We were able to show decreases in clusterin levels in the majority of patients during the first 4 weeks of therapy, suggestive of biological activity of the antisense oligonucleotide. However, we did not observe a relationship between the magnitude of the percent decrease in serum clusterin levels and objective response. This may in part be due to the limited sample size, the relatively early time correlation of serum clusterin (day 22) with response, as well as only five patients having a documented response.

Docetaxel is one of the most active chemotherapeutic agents used in both early-stage and advanced stage breast cancer. Phase II and III studies have shown a dose-response relationship for both efficacy and toxicity. As well, efficacy can be dependent on the degree of prior systemic therapy (particularly chemotherapy) that patients enrolled on the trial had previously received. Initial phase II and III studies of docetaxel at 100 mg/m^2 as second-line therapy in metastatic breast cancer yielded response rates of ~50% (19–21). A phase II trial of docetaxel at 75 mg/m^2 as second-line therapy showed an overall response rate of 33% (22). Lastly, in a large phase III trial in 527 women with metastatic breast cancer, docetaxel as second-line therapy at three different doses (60, 75, and 100 mg/m^2) produced response rates of 22.1%, 23.3%, and 36%, respectively (23). This trial was designed to detect a response rate of interest of 55% for the combination of OGX-011 and docetaxel 75 mg/m^2. We did not believe a response rate of ≤35% would be sufficiently interesting to pursue, given the results of other phase II and III trials. The observation of 5 of 15 patients with objective response failed to meet the criteria to continue to the second stage of accrual. With this small final sample size, however, the confidence intervals around the observed 33% response rate are wide (11.8-61.6%).

In conclusion, OGX-011 delivered as monotherapy and in combination with docetaxel was well tolerated. The toxicity profile was similar to that of single agent docetaxel, except for the transient fever and rigors also seen with other antisense molecules (24, 25). Clinical activity was seen with this combination in a minimally pretreated population of women with metastatic breast cancer; however, the documented response rate seemed to be similar to that from single agent docetaxel, and as such the trial did not meet the criteria to proceed to the second stage of accrual. Randomized phase II designs of combinations of novel agents and active therapy with the utilization of biological end points rather than standard response criteria may prove more informative than a traditional single arm trial. A better understanding of the biology of resistance to taxanes may aid in further development of targeted agents to enhance the activity of this important chemotherapeutic class.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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